STEM CELLS

Equal opportunities in stemness

Tissue renewal requires proliferative progenitors with long-lasting potential. Designated stem cells within specialized niches are considered to be the primary mechanism for this requirement. Recent studies show that dispersed equipotent progenitors are sufficient to account for fast-paced cellular dynamics in skin oil glands and foetal gut epithelium.

Qing Nie and Maksim V. Plikus

To maintain a stable steady state, tissues with a high rate of cellular wear and tear require fast mitotic activity from their progenitors. Thus, robust mechanisms for long-term preservation of the progenitor state are required to avoid progenitor exhaustion and tissue collapse. One such strategy is to designate groups of specialized stem cells into anatomic niches whose signalling environment supports stemness (Fig. 1). Commonly, such designated stem cells divide infrequently to produce short-lived, transit-amplifying progeny that in turn divide rapidly to generate new differentiated cells for the tissue[1]. Transit-amplifying cells often relocate into their own distinct signalling microenvironment, which supports fast division and differentiation, but not stemness. This tissue organization strategy is fairly prevalent, and examples include hair follicles, in which stem cells reside in the bulge[2], and the small intestine, in which stem cells are located at the crypt base[3].

An alternative strategy, however, exists in some other fast-renewing tissues. For example, in skin epidermis, a clear distinction between long-lasting cells and rapidly dividing cells is lacking in terms of their anatomic distribution, cell cycle properties, and marker genes (Fig. 1). Indeed, skin epidermis is maintained by so-called equipotent progenitors[4] that proliferate at a high rate and also produce long-lasting clones, a key property of stem cells. At the population level, equipotency allows a tissue to remain in a steady state, whereas at the individual level some cellular clones expand and others shrink and even disappear, a phenomenon known as neutral drift[1]. When such clonal competition occurs in small, isolated tissue compartments, one clone eventually outcompetes the others, a phenomenon known as monoclonal conversion[1].

In a study in this issue of *Nature Cell Biology*, Andersen et al.[5] examined whether skin oil glands, also called sebaceous glands, are maintained by designated stem cells or by equipotent progenitors. These glands are functionally distinct units of the skin tasked with producing a lipid-rich secretion that waterproofs and protects skin from the outside. Lobe-like in shape, sebaceous glands are intimately connected to hair follicles via ducts. Yet, unlike hair follicles, they do not undergo obvious growth cycles and instead constantly output their secretion[6]. Previous lineage studies provided evidence both for equipotent progenitors residing within the gland[7] and for designated stem cells near[8,9] and outside the duct[10], which send short-lived progeny

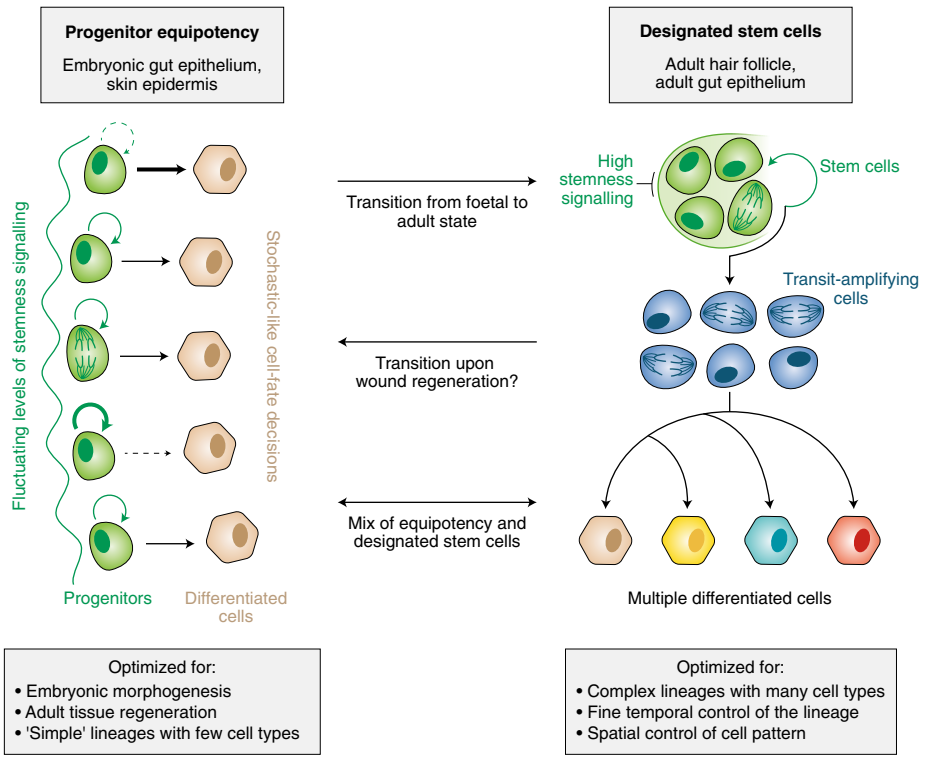

Fig. 1 | Equipotency and designated stem cells as complementary strategies for lineage maintenance. Long-term tissue maintenance can be accomplished with either many dispersed equipotent progenitors (left) or rare designated stem cells residing in specialized niches (right). Evolved to divide infrequently and persist long-term, designated stem cells give rise to transit-amplifying progeny (blue on the right) that move out of the niche, where they rapidly proliferate and differentiate, often into multiple cell types. With equipotency, tissue is maintained by many actively dividing and, simultaneously, long-lasting progenitors. While in their niches, stem cells self-renew efficiently as a result of specialized signalling. Self-renewal of equipotent progenitors is stochastic-like, a phenomenon caused by fluctuating soluble, extracellular matrix and cell–cell contact cues in the extracellular 'information space' (zigzag green line on the left). Each lineage maintenance strategy has its distinct advantages (text boxes at the bottom). Further, strategies can switch during tissue development and regeneration and also are likely to complement each other.

into the gland. By quantifying fate-mapping outcomes in vivo and correlating them with mathematical model predictions on clone size dynamics, the authors concluded that the steady-state renewal of sebaceous glands in adult mice occurs via equipotent basal progenitors independently of neighboring stem cell populations. Single-cell fate-mapping assays, in which one progenitor per gland was marked at the beginning of an experiment, supported this conclusion and showed progressive monoclonal conversion of glands. In these assays, labeled cell clones lacked clear directional bias, suggesting that clonogenic gland progenitors are equally distributed. Experimentally measured clonal data were most consistent with simulations of a mathematical model that assumes an equipotent population of dividing progenitors stochastically choosing between alternative fates: to differentiate or divide into two new progenitors.

Another recent study in *Nature* shows that intestinal epithelial progenitors remain equipotent during the phase of foetal gut morphogenesis and prior to the establishment of adult villus–crypt anatomy[11]. The foetal intestinal epithelium in mice first becomes patterned into primordial villi, which then rapidly increase in number via the process of villification during late embryonic and early postnatal periods, reaching adult villi density by approximately day five after birth[11]. Rather than exclusively forming in the intervillus space, many new villi develop via fission of earlier-born villi coupled with lateral cell rearrangements across neighboring villi and intervillus regions. Under such a mechanism, all foetal intestinal progenitors, irrespective of their initial anatomic position, have equal opportunity to become adult intestinal stem cells of the crypt, and their final fate is determined by the ultimate anatomic position that cells assume at the end of villification. Thus, it seems that maintaining equipotency, or at least making early fate choices more easily reversible, is crucial for normal gut morphogenesis.

Considering that both strategies have been observed during the formation and maintenance of different tissues, what benefits does each strategy offer? So far, equipotency has been the primary mechanism observed in expanding tissues with highly curved spatial structures, such as the developing gut[11]. Only an equipotency model faithfully recapitulates the progressive morphogenesis of new villi across the entire foetal gut, including the tips of preexisting villi. A similar strategy likely operates during hair morphogenesis in foetal skin: new hair primordia form from embryonic epidermal progenitors via self-organized patterning with no apparent restrictions on the spatial placement of primordia[12]. Similarly to morphogenesis, regeneration might also benefit from progenitor equipotency to enhance robustness. By reactivating an embryonic-like program, the epidermis in large skin wounds can regenerate new hair follicles without fully relying on lineage contribution from preexisting hair-follicle-fated stem cells[13]. With equipotency, the basal epidermal progenitors in skin wounds are likely to be able to make new hair follicles irrespective of their prior lineage identity in unwounded skin. Beyond morphogenesis and wound repair, equipotency can be a preferred mode of organization for relatively simple lineages, such as epidermal or sebaceous gland lineages, in which the number of cell types is small and their relationship is linear.

Conversely, the existence of designated and spatially segregated stem cells can be beneficial for complex lineages, consisting of many branching points and multiple terminally differentiated cell types, as found in the hair follicle and adult intestine. Spatial segregation of stem cells away from their progeny can localize differentiation-promoting signalling without interfering with the stem cell niche signalling. Notably, major differentiation events in the hair-follicle lineage occur at its base, in the so-called hair matrix, and at a distance from the bona fide stem cell niche. Another benefit that designated stem cells in specialized niches may offer is to gain stronger, on-demand temporal control over lineage production. For example, placing hair follicle stem cells into a spatially defined and quiescent signal-enriched niche allows for extended, often months-long resting phases between active hair growth cycles[14]. This adaptation potentially provides animals with an energy conservation advantage. Functional fur can consist entirely of old hairs without requiring a constant resupply of newly growing hairs. Such extended quiescence might be more difficult to enforce on many equipotent progenitors interspersed in space. Although both strategies may provide different benefits for different purposes, there is a possibility that they may coexist. In support of this theory, a recent study by Feldman et al.[9] argued for the existence of previously debated BLIMP1$^+$ sebaceous gland stem cells[7,8,10] by showing that in vitro–differentiated sebaceous gland organoids form with high efficiency from single BLIMP1$^+$ cells, which also maintain long-term passaging potential.

What drives the cellular decision to differentiate or renew? The study by Andersen et al.[5] also sheds light on the potential mechanism that drives decision making in an equipotent progenitor population. Mathematical modelling convincingly argues that stochastic cell-fate decisions can be predicted using parameters such as division rate and fate probability, which are sufficient to faithfully account for the observed steady-state renewal of sebaceous glands by equipotent progenitors. During tissue morphogenesis or regeneration, the values of such parameters must be dynamically adjusted as required to regulate differentiation versus self-renewal. Feedback regulation imposed on progenitor cells by their environment may potentially robustly control these parameters[15].

Intriguingly, the authors also performed experiments with oncogene-overexpressing mice in which sebaceous glands were substantially enlarged, driven by gland progenitors biasing toward self-renewal[5]. Concurrent with gland enlargement, stiffness and molecular composition of the surrounding extracellular matrix changed prominently. An open question is whether the underlying extracellular matrix provides biophysical and signalling inputs to progenitors to guide their decisions. Interestingly, a recent study by Liu et al.[16] showed that levels of collagen XVII in the basement membrane of skin epidermis naturally fluctuate, in part as a result of proteolysis, and epidermal progenitors exposed to high collagen XVII levels commonly self-renew by dividing parallel to skin plane. Conversely, those subjected to decreased collagen XVII preferentially divide perpendicularly, and their clones are reduced and outcompeted over time.

Overall, these observations suggest that a stochastic-like fate selection by individual equipotent progenitors may be underpinned by complex inputs to cells from their 'information space', which may include the extracellular matrix, cell–cell contact cues and soluble growth factor signals from neighboring cells, including other progenitors and immune cells (Fig. 1). Highly curved spatial structures, such as the gut, are particularly suitable to provide strong physical and mechanical cues to the progenitors. Future studies that simultaneously measure cellular dynamics with one or several information inputs, preferably at single-cell resolution, will advance our understanding on cell-fate control in equipotency. In addition, skin—with its many layers and patterned structures—offers a particularly fertile system for conducting multiscale mathematical modelling to dissect cell-fate control[17]. The study by Andersen et al.[5] provides a prime successful example on how the synergy between modelling and

experimentations leads to new discoveries in stem cell biology. ❐

Qing Nie[1,2,3,4] and Maksim V. Plikus[1,2,4,5]
[1]*NSF-Simons Center for Multiscale Cell Fate Research, University of California, Irvine, Irvine, CA, USA.* [2]*Center for Complex Biological Systems, University of California, Irvine, Irvine, CA, USA.* [3]*Department of Mathematics, University of California, Irvine, Irvine, CA, USA.* [4]*Department of Developmental and Cell Biology, University of California, Irvine, Irvine, CA, USA.* [5]*Sue and Bill Gross Stem Cell Research Center, University of California, Irvine, Irvine, CA, USA.*
e-mail: qnie@uci.edu; plikus@uci.edu

Published online: 29 July 2019
https://doi.org/10.1038/s41556-019-0366-6

References

1. Krieger, T. & Simons, B. D. *Development* **142**, 1396–1406 (2015).
2. Cotsarelis, G., Sun, T. T. & Lavker, R. M. *Cell* **61**, 1329–1337 (1990).
3. Cheng, H. & Leblond, C. P. *Am. J. Anat.* **141**, 537–561 (1974).
4. Clayton, E. et al. *Nature* **446**, 185–189 (2007).
5. Andersen, M. S. et al. *Nat. Cell Biol.* https://doi.org/10.1038/s41556-019-0362-x (2019).
6. Hinde, E. et al. *Exp. Dermatol.* **22**, 631–637 (2013).
7. Füllgrabe, A. et al. *Stem Cell Rep.* **5**, 843–855 (2015).
8. Horsley, V. et al. *Cell* **126**, 597–609 (2006).
9. Feldman, A. et al. *Nat. Commun.* **10**, 2348 (2019).
10. Kretzschmar, K. et al. *Stem Cell Rep.* **3**, 620–633 (2014).
11. Guiu, J. et al. *Nature* **570**, 107–111 (2019).
12. Glover, J. D. et al. *PLoS Biol.* **15**, e2002117 (2017).
13. Ito, M. et al. *Nature* **447**, 316–320 (2007).
14. Plikus, M. V. et al. *Science* **332**, 586–589 (2011).
15. Lo, W. C. et al. *Math. Biosci. Eng.* **6**, 59–82 (2009).
16. Liu, N. et al. *Nature* **568**, 344–350 (2019).
17. Wang, Y. et al. *Exp. Dermatol.* **28**, 493–502 (2019).

Competing interests

The authors declare no competing interests.

COMMUNICATIONS BIOLOGY

NOW PUBLISHING CONTENT

A new open access journal for the biological sciences from Nature Research

Communications Biology publishes high-quality primary research articles, reviews and commentary in all areas of the biological sciences. Papers published in the journal represent significant advances that bring new insight to a specialized area of research.

All papers are handled by experienced in-house professional editors supported by an expert Editorial board.

Submit your research today and benefit from:

- Thorough peer review
- Fast decision process
- High Nature editorial standards
- High visibility
- CC-BY open access as standard

@commsbio nature.com/commsbio natureresearch

A48164